



REVIEW

Reperfusion injury in acute myocardial infarction: From bench to cath lab. Part II: Clinical issues and therapeutic options

Lésions myocardiques de reperfusion au cours de l'infarctus myocardique aigu du laboratoire au « cath-lab ». Section II : aspects cliniques et options thérapeutiques

Jean-Pierre Monassier*

Cardiology Department, Emile Muller Hospital, 20, Laennec Street, 68000 Mulhouse, France

Received 10 March 2008; received in revised form 26 May 2008; accepted 6 June 2008
Available online 27 September 2008

KEYWORDS

Modified reperfusion;
No-reflow;
Postconditioning;
ST-segment
resolution;
Thrombus aspiration

Summary Two forms of reperfusion injury can occur in patients with ST-segment elevation acute myocardial infarction who are undergoing primary angioplasty: no-reflow phenomenon and reperfusion syndrome. No-reflow, defined as low or no distal perfusion despite removal of epicardial occlusion, can be detected by angiographic flow, myocardial blush grade and contrast echocardiography. Reperfusion syndrome involves haemodynamic and rhythmic disturbances, but an overall paradoxical ST-segment increase. A variety of mechanisms give rise to no-reflow, including distal embolization, leucocyte plugging and vasoconstriction. Reperfusion syndrome reflects, at least in part, the cardiomyocyte component of reperfusion injury. Reperfusion injury can be predicted from the initial electrocardiogram, especially when QRS complex distortion is observed. Pharmacological prevention of reperfusion injury has been tested in a number of trials; the most useful drugs available currently are glycoprotein IIb/IIIa receptor blockers and adenosine. Thrombus aspiration leads to faster and greater ST-segment resolution. Postconditioning (also called staccato reperfusion) is a new strategy that has produced highly encouraging results, although it has been tested only in a small randomized study. New tools are required to enable thrombus aspiration and postconditioning to be carried out simultaneously. Pharmacological postconditioning can be anticipated in the

* Fax: +33 3 89 64 71 84.

E-mail address: monassierj@ch-mulhouse.fr.

MOTS CLÉS

Aspiration du thrombus ;
No-reflow ;
 Postconditionnement ;
 Reperfusion modifiée ;
 Résolution du segment ST

near future, as many drugs appear to achieve the same positive effect as mechanical modified reperfusion.

© 2008 Elsevier Masson SAS. All rights reserved.

Résumé Les lésions de reperfusion au cours de l'infarctus du myocarde aigu traité par angioplastie primaire se présentent sous deux aspects : le *no-reflow* et le syndrome de reperfusion. Le *no-reflow* se définit comme l'absence ou le ralentissement du flux distal alors que l'obstacle épigardique a été levé. Le syndrome de reperfusion associe des modifications hémodynamiques et rythmiques mais est surtout marqué par une majoration paradoxale du sus-décalage de ST. Le *no-reflow* est détecté notamment par angiographie conventionnelle ou par échographie de contraste. Il est dû à un ensemble de mécanismes (embolies distales, agrégats leucocytaires, vasoconstriction, etc.). Le syndrome de reperfusion exprime au moins en partie la composante cardiomyocytaire des lésions de reperfusion. La survenue de ces lésions peut être prédite à partir de l'électrocardiogramme initial et notamment en présence d'un aspect de distorsion de QRS. De nombreux essais de prévention pharmacologiques ont été réalisés. Les molécules les plus efficaces et dès à présent utilisables sont les antiglycoprotéines IIb/IIIa et l'adénosine. L'aspiration du thrombus permet une régression plus rapide et plus importante du sus-décalage de ST. Le postconditionnement mécanique appelé également reperfusion « staccato » s'est montré efficace dans une première petite étude randomisée mais permet de réels espoirs. Pour combiner l'aspiration du thrombus et le postconditionnement simultanément de nouveaux outils sont nécessaires. Par ailleurs l'espoir de pouvoir mettre en œuvre un postconditionnement pharmacologique dans un proche futur est réel.

© 2008 Elsevier Masson SAS. All rights reserved.

Abbreviations

ATP	Adenosine triphosphate
ECG	Electrocardiogram
IMR	Index of microvascular resistance
LVF	Left ventricular function
MBG	Myocardial blush grade
MCE	Myocardial contrast echocardiography
MTP	Mitochondrial transition pore
NR	No-reflow
pPCI	Primary percutaneous coronary intervention
PVF	Peak volume flow
RISK	Reperfusion injury salvage kinase
ROS	Reactive oxygen species
TFC	Thrombolysis in myocardial infarction frame count
TIMI	Thrombolysis in myocardial infarction

Background

Experimental data have shown that the final myocardial outcome of an 'ischemic–reperfusion' sequence depends not only on the time delay between occlusion and reperfusion but also on whether lethal reperfusion injury occurs (see Part I).

Despite the early description of reperfusion syndrome [1–3] and stunned myocardium phenomenon [4], for many years interventional cardiologists failed to acknowledge the concept of lethal reperfusion injury and the reality of its existence in humans. The occurrence of no-reflow (NR) during primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) was first

described by Krug et al. in 1966 [5], and later by Kloner et al. in 1974 [6], in ischaemia–reperfusion experimental animal models in which coronary occlusion was achieved by ligation without any thrombotic material. Nevertheless, interventional cardiologists continued to regard NR as a technical failure caused by thrombus fragmentation and distal embolism [7,8].

The first positive report of pharmacologically modified reperfusion (using perfluorochemicals) failed to catch the attention of interventional cardiologists [9], as did the surprising results of the Primary Angioplasty in Myocardial Infarction (PAMI) stent study, in which stented patients had a slightly poorer clinical outcome [10]. The failure of, and unconvincing results from, numerous drug trials [11] reinforced the belief that the principal problem during pPCI was vascular, requiring embolism and spasm prevention [12]. However, the first randomized study into postconditioning in humans [13] altered the opinion of interventional cardiologists, who started to accept that a useful link might be made between laboratory research and reperfusion in humans, and that modified reperfusion might have a role in the catheterization laboratory (cath lab). The aim of this review is to demonstrate how experimental modified reperfusion might influence routine pPCI practice in humans.

In an attempt to clarify this complex phenomenon, it is useful to separate the two facets of reperfusion injury – one involving the endothelium and hence postreperfusion flow, and the other involving cardiomyocytes (Fig. 1). Nevertheless, these two consequences of the sudden reopening of the artery are closely interconnected and therapeutic options must target them both. Reopening of the artery is essential to save the myocardium; prevention and treatment of reperfusion injury is the next challenge in the quest to optimize the final outcome.

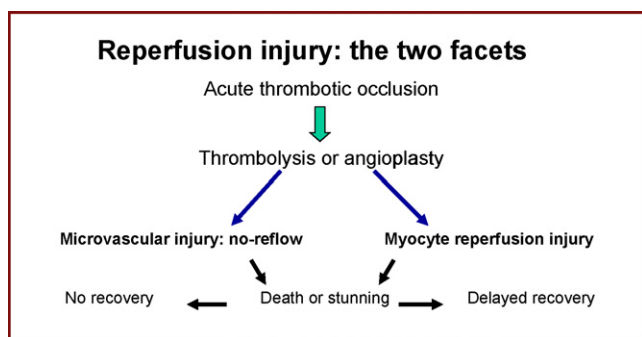


Figure 1. The two facets of reperfusion injury, involving endothelium and cardiomyocytes.

The no-reflow phenomenon

First reported 20 years ago after thrombolytic therapy using scintigraphy [14], and again one year later using angiography [15], NR is defined as the absence of or poor myocardial perfusion despite the removal of the epicardial artery obstruction. Numerous techniques can be used to assess this problem. A final Thrombolysis In Myocardial Infarction (TIMI) of grade less than 3 flow is seen with angiography, extending from no-flow to slow-flow, despite the occlusion having been removed with no residual obstacle or vessel dissection [7,16]. The incidence of NR, judged on the basis of the initial TIMI classification, is around 10–15%. The effective myocardial perfusion can be measured more accurately using the TIMI frame count (TFC) [17], which is defined as the number of frames required for dye to reach the distal artery; NR is considered when the TFC is greater than 40 frames [17].

The gold standard measure of myocardial reperfusion is myocardial blush grade (MBG) [18]: MBG 0 is defined as no myocardial opacification; MBG 1 as myocardial opacification without any dye clearance; MBG 2 as myocardial opacification with slow clearance; and MBG 3 as myocardial opacification with quick clearance. Only 21% of patients who reached TIMI grade 3 flow after pPCI had MBG 3. Using conventional angiographic TIMI grade flow assessment, Anderson et al. showed that only TIMI grade 3 flow could be considered to be an indicator of successful reperfusion [19]. MBG is the most powerful predictor of prognosis [20]. Going from MBG 0 to 3, 30-day mortality has been shown to decrease from 6.2 to 5.1%, 4.4 and 2.0%, respectively, in patients with heart failure at presentation [21], with MBG 0 and 1 associated with the worst 400-day follow-up prognosis [21]. Taken together, these data encourage interventional cardiologists not only to achieve but also to go beyond TIMI grade 3 flow [22].

Myocardial contrast echocardiography (MCE) has shown NR to be present in patients even if they have reached angiographic TIMI grade 3 flow; NR was observed in 16–40% of such patients and in 100% of those with TIMI grade 2 flow [23]. Prognosis is linked directly to MCE reflow [24]. Galiuto et al. found that even in patients with TIMI grade 3 flow, a contrast defect greater than 25% was the most accurate predictor of left ventricular remodelling – better than MBG or ST – segment resolution [25]. The degree of contrast defect is linked closely to ST-segment decrease.

Santoro et al. found that the ST-segment decreased by more than 50% in 77% of patients with reflow compared with by 10% in patients with echo NR [26]. Combining MBG and ST-segment resolution makes it possible to predict early and late left ventricular function (LVF) recovery [27]. The combination of MBG 2 or 3 with an ST-segment decrease of more than 50% has been shown to produce seven-day and six-month LVF recovery rates of 65 and 95%, respectively. By comparison, MBG 2 or 3 and an ST-segment decrease of less than 50% resulted in seven-day and six-month LVF recovery rates of 24 and 86%, respectively. In patients with neither MBG 2 or 3, nor an ST-segment decrease, the seven-day and six-month LVF recovery rates were 18 and 32%, respectively.

It may be possible to detect NR 'on-line' using a new measure – the index of microvascular resistance (IMR) [28]. Using a pressure sensor wire (as for fractional flow measurement), after injection of adenosine, an IMR greater than 32 units was predictive of poor LVF recovery at three-month follow-up.

NR can also be assessed by intracoronary Doppler flow, with average peak velocity and early systolic retrograde flow correlating well with MCE defect [29], and by magnetic resonance imaging [30–33]. Positron tomography, like magnetic resonance imaging, is a technique that will be developed in the future [34], especially for therapeutic trials. Feldman et al. found a good correlation between coronary flow reserve immediately after pPCI and ST-segment recovery [35]. The criteria defining NR, depending on the assessment technique used, are summarized in Fig. 2.

ST-segment decrease is probably linked to NR, but also depends on cardiomyocyte damage. By pooling the results of two studies comparing MBG and ST-segment resolution [18,27], it is possible to identify four different profiles after pPCI (Fig. 3), providing confirmation that endothelial and cardiomyocyte responses to reperfusion do not always evolve in parallel. The four different profiles are as follows:

- flow recovery with ST-segment resolution;
- flow recovery without ST-segment resolution;
- low-reflow or NR without ST-segment resolution;

• Epicardial angiography:

*TIMI 0-2

• Myocardial blush grade angiography:

*grade 0-1

• Contrast echocardiography:

*>50 % area at risk

• Endocoronary Doppler:

*reverse systolic flow

*quick diastolic deceleration time

*coronary flow reserve <1.6

Figure 2. Definition of NR according to assessment technique used.

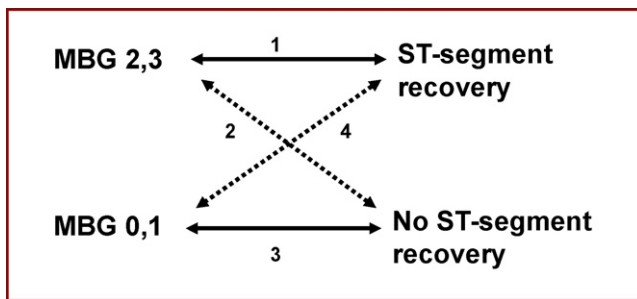


Figure 3. Discrepancies between angiographic NR definition and ST-segment resolution: ideal postreperfusion flow is most often (1) but not always (2) predictive of ST-segment resolution, and vice versa (3,4).

- ST-segment recovery despite low-reflow or NR. These conflicting characteristics highlight the two facets of reperfusion injury – endothelial and myocardial.

The time course of NR must be taken into account. Studies in animals have shown that even after early hyperaemia [36] there is a progressive loss of infarct perfusion [36–38]. Twenty years ago, Ambrosio et al. found that after two minutes of reperfusion in a dog model, the area of impaired reperfusion averaged $9.5 \pm 3.0\%$, whereas it was three times as large after 3.5 h of reperfusion ($25.9 \pm 8.2\%$) [36]. Few studies have been done in humans to address this evolutive aspect of NR. Tsunoda et al. observed two different groups who had reached angiographic TIMI grade 3 flow [39]. One group experienced an early decrease in average peak velocity followed by a late recovery, while the other experienced a continuous decrease in average peak velocity; the late recovery group showed a greater improvement in LVEF.

It is now evident that the different tools that can be used to assess the efficacy of myocardial reperfusion after pPCI show that NR exists in a large number of patients who have a good immediate angiographic result. Classic TIMI grade 3 flow is required, but is not sufficiently accurate to distinguish between distal reflow and NR.

The mechanisms of NR are well elucidated, and include distal embolism, leucocyte and platelet plugging, microvascular spasm, capillary swelling and external compression by hypercontracted cardiomyocytes [34]. A variety of clinical and biological variables may predict the occurrence of NR; these include initial hyperglycaemia [40–42], high leucocyte count [43], troponin elevation at presentation [44], longer time delay, anterior infarcts [45] and lack of preinfarction angina [46].

Cardiomyocyte reperfusion injury

While interventional cardiologists have paid heed to the angiographic results of pPCI, less focus has been placed on the deleterious effects of reperfusion on cardiomyocytes. Stunned myocardium [4] has long been considered to be a reflection of the time needed to repair ischaemic damage rather than a consequence of reperfusion injury.

Reperfusion syndrome [3] combines cardiac arrhythmias such as accelerated idioventricular rhythm, severe bradycardia, arterial pressure drop leading in rare cases to electromechanical dissociation [2], chest pain paroxysm and ST-segment elevation increase [1] (Fig. 4). ST-segment monitoring during and immediately after culprit artery desobstruction might provide useful information about the

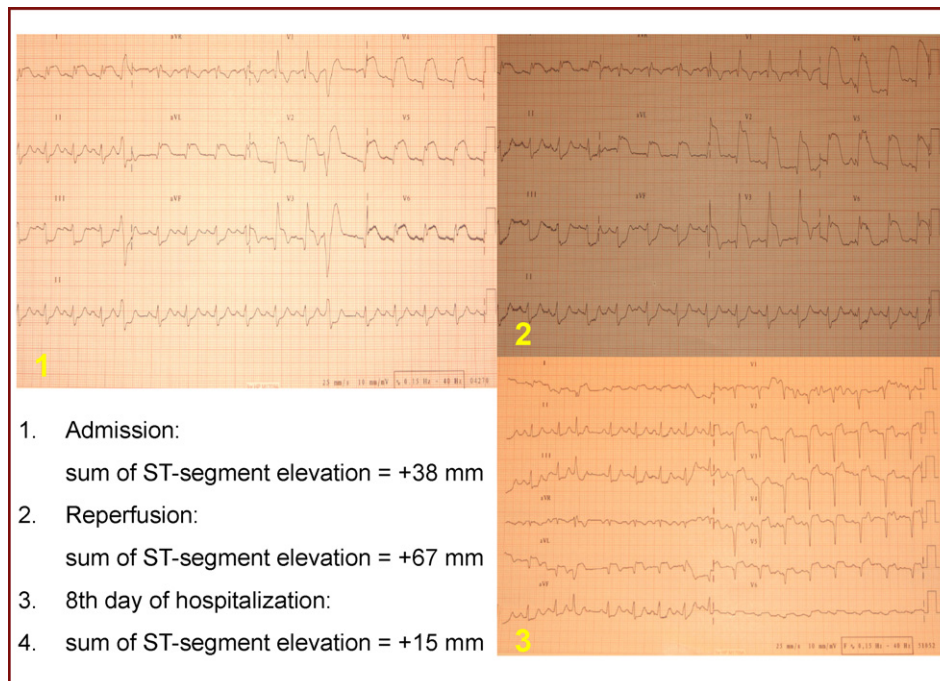


Figure 4. Paradoxical ST-segment increase at reperfusion in acute anterior ST-segment elevation acute myocardial infarction treated with pPCI: (1) initial ECG with QRS distortion (grade 3); (2) immediately postflow ECG with sudden major increase in ST-segment elevation; (3) slow and delayed ST-segment recovery.

myocardial response to reoxygenation. An increase in ST-segment shift may be caused by ionic cellular mechanisms such as potassium efflux (see Part I). A paradoxical increase in chest pain and ST-segment elevation can occur immediately after the reopening of the artery or a few minutes later [1]. The fact that even with MBG 3, the ST-segment does not improve in around 15% of patients, supports the existence of two facets of reperfusion injury – vascular and cellular [18]. Santoro et al. tried to differentiate between NR and cardiomyocyte reperfusion injury [26]. Eleven of 37 patients (29.7%) treated with pPCI experienced MCE NR. A sudden postreperfusion ST-segment increase of more than 30% occurred in 10 patients (27.0%), including three of 26 (11.5%) with MCE reflow compared with seven of 11 (63.6%) with MCE NR, which shows that cellular mechanisms can cause the ST-segment to deteriorate even in the presence of reflow. Nevertheless, the additional ST-segment increase was of shorter duration in the reflow group than in the NR group.

Thus, the components of reperfusion injury are clearly interwoven and angiographic reflow must be combined with immediate ST-segment shift after pPCI (Fig. 2) [47].

Initial electrocardiogram and reperfusion injury

The initial electrocardiogram (ECG) is a reliable predictor of ST-segment and angiographic outcome after pPCI. The

greater the sum of ST-segment elevation in acute anterior infarctions, the worse the ventricular prognosis as a result of severe ischaemia and reperfusion injury [48,49]. Kurisu et al. found a sum of ST-segment elevation greater than 10mm to be an appropriate cut-off value [49]. Patients with less severe ST-segment elevation presented more frequently with prodromal angina and may therefore have been protected by preconditioning [49]. Greater ST-segment elevation in the D1 lead than in the aVL lead is associated with impaired myocardial reperfusion (assessed by MBG) and less myocardial salvage in patients with recanalized anterior infarctions [50], as well as with ST-segment depression in the aVR lead in patients with acute inferior infarctions [51]. In patients with inferior infarctions, a larger sum of ST-segment depression in the V4–V6 leads than in the V1–V4 leads is also considered to be a marker of poor prognosis, although a clear relationship with reperfusion injury has not been established [52].

The most studied feature of the initial ECG is QRS complex distortion [52–54]. The initial ECG can be categorized as follows on the basis of repolarization: grade I, T-wave peaking; grade II, ST-segment elevation without distortion of the terminal portion of QRS complex; grade III, ST-segment elevation with distortion of the QRS complex, defined as disappearance of the S wave in the VI–V3 leads or appearance of ST-segment elevation (measured at the J point) greater than 50% of the R wave in the same lead (Fig. 5). A grade III ECG can be observed in around 30% of patients [52] and predicts a poorer prognosis despite infarct-related

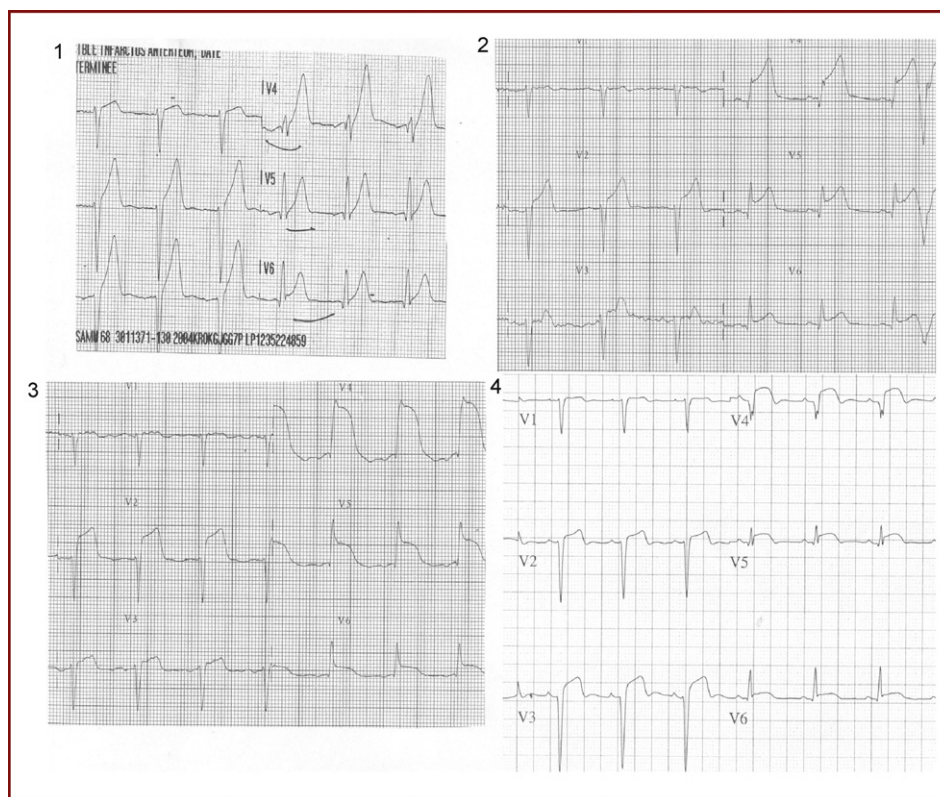


Figure 5. Early (day of hospitalization) anterior infarct: progressive evolution from (1) initial grade 1 ECG (prehospital recording), to (2) grade 3 with distortion (initial ECG in cath lab), to (3) sudden increase in ST-segment after pPCI and (4) slow recovery one hour later in coronary care unit.

artery reopening, due to more frequent NR and less frequent ST-segment decrease as a consequence of reperfusion injury.

It is clear, therefore, that admission ECG and ST-segment changes after pPCI may be valuable predictors and markers of global reperfusion injury. Immediate ST-segment changes after pPCI can be used reliably to unmask reperfusion injury, which in turn enables appropriate modifications to be made to the reperfusion strategy; given the association of reperfusion injury with mortality rate and final LVEF, this measure may emerge as a strong surrogate endpoint in future clinical trials.

Therapeutic options

Unexpected failures

Following robust experimental results, a variety of molecules have been tested for their ability to counteract either NR or cardiomyocyte reperfusion injury; of these, reactive oxygen species (ROS) scavengers [55], inhibitors of the sodium-hydrogen exchanger [56] and inhibitors of the inflammatory cascade [57–59] have failed to produce significant benefits. The reasons for these surprisingly negative results cannot be discussed in detail here and for each type of molecule, but may include the multifactorial mechanisms of reperfusion injury and the need for these mechanisms to be acted upon simultaneously, the intravenous mode of drug delivery, the timing of delivery (during ischaemia or during reperfusion), the gap between the experimental setting and STEMI in humans, and the low risk level of patients included in the studies.

The therapeutic options discussed below have all produced some positive results and are either available for immediate use or are under development for future use.

Thrombectomy and filter devices

Given that distal embolization is one of the causes of NR [60], various devices have been proposed for use in the removal of thrombi or the prevention of distal embolisms into arterioles and small coronary branches. Numerous small trials have demonstrated the efficacy of these devices in terms of improved flow and ST-segment regression; MBG 3 can be reached in around 85% of patients compared with 45% after conventional pPCI, and immediate complete ST-segment regression is noted in around 70% of patients compared with 50% after conventional pPCI [12,61–63]. Nevertheless, in a meta-analysis of 14 trials, antiembolic tools had no effect on major clinical endpoints (deaths and reinfarction) [64]. This finding does not mean that these devices are not useful, but is a reflection of the fact that distal embolisms are only one component of reperfusion injury and NR. Furthermore, in each of these trials, the death rate was too low to enable an effect on mortality to be assessed.

The extent of ST-segment resolution is a strong predictor of mean and long-term prognosis [65], and positive results using this criterion as a surrogate endpoint may be indicative of a beneficial impact of thrombectomy devices on long-term clinical events. Account must also now be taken of a recent randomized trial that included more than 1000

patients and compared thrombectomy with stenting alone; the thrombectomy group had a significantly better MBG, more frequent complete ST-segment resolution and a lower death rate [66]. Thus, thrombectomy devices have an important role to play, especially in patients with high thrombus burden [67], although they are probably unable to achieve the therapeutic goal when used in isolation.

Glycoprotein IIb/IIIa receptor blockade

Abciximab has been tested widely and positively as an adjunctive therapy before and during pPCI; its efficacy is due to an antithrombotic effect, preventing subacute stent thrombosis, but is also attributable to an improvement in distal flow. This non-specific drug interacts not only with platelets (decreasing platelet reactivity, aggregates, plugging and embolization) but also inhibits platelet–leucocyte interaction and hence the cytotoxic inflammatory response [68–71]. Abciximab is even more effective when initial platelet volume is greater than 10.3 fl [72]. Hence abciximab, due to its non-specific action on platelets and leucocytes, is a logical adjunct to pPCI. Neumann et al. showed an improvement in peak volume flow (PVF) in STEMI patients treated with pPCI, stents and abciximab [68]; PVF averaged 18.1 cm/s (13.6–22.6) compared with 10.4 cm/s (5.4–15.4) in patients who did not receive abciximab ($p=0.024$). A similar decrease in the incidence of NR with abciximab was observed when evaluating microvascular permeability with contrast echocardiography [69].

Adenosine

Adenosine is an endogenous nucleoside produced by the degradation of adenosine triphosphate (ATP) [73]. In a normal physiological setting it is present in a 40-fold greater concentration in endothelial cells, whereas myocytes become the major source of adenosine during ischaemia due to the inability of mitochondria to rephosphorylate adenosine diphosphate and adenosine monophosphate. Adenosine is a ubiquitous molecule that promotes a variety of metabolic effects; it acts on all the reperfusion injury mechanisms (with the exception of distal embolism), promoting preservation of microvascular flow, inhibiting neutrophils and the inflammatory cascade, reducing ROS synthesis and stabilizing cellular membranes, restoring calcium homeostasis and mediating postconditioning (see below) [73]. Marzilli et al. showed that the intracoronary injection of adenosine before reperfusion (using a small perfusion balloon settled distally) prevents NR [74]. In a randomized study involving 44 patients, NR occurred in only one patient (3.7%) who received adenosine compared with 25.9% of patients in the control group ($p=0.04$).

Three large, randomized trials of adenosine have been reported. The Acute Myocardial Infarction Study of Adenosine (AMISTAD) was performed in 236 patients with anterior and inferior infarctions [75]. Patients received thrombolytic therapy plus adenosine 70 µg/kg per min or placebo for three hours. At day 6 an isotopic reduction in infarct size was seen in the adenosine group; the reduction was greatest in patients with an anterior infarct.

The Attenuation by Adenosine of Cardiac Complications (ATTACC) study was a prospective, large-scale, random-

ized, placebo-controlled study using a low adenosine dose ($10\text{ }\mu\text{g/kg}$ per min) infused intravenously for six hours in patients undergoing thrombolysis [76]. At the six-month follow-up of 292 patients with anterior infarcts, the adenosine group showed a trend for less all-cause mortality (8.4% versus 15.3%; $p=0.07$) and cardiovascular mortality (8.4% versus 14.6%; $p=0.08$). Furthermore, in a post hoc analysis of a subgroup with anterior infarcts and severely depressed LVEF, the six-month death rate was significantly lower in the adenosine group (2.0% versus 12.1%; $p=0.007$).

Finally, the Acute Myocardial Infarction Study of Adenosine II (AMISTAD-II) was a double-blind, placebo-controlled, randomized study in 2118 patients with anterior STEMI undergoing thrombolysis or pPCI [77,78]. Two doses of adenosine were tested: 50 and $70\text{ }\mu\text{g/kg}$ per min. Despite the lack of difference between the two groups in terms of major clinical endpoints, a marked reduction in infarct size was observed in the high-dose group. In a post hoc analysis, among patients receiving reperfusion therapy within three hours of symptoms, adenosine reduced one-month and six-month mortality rates significantly: 5.2% versus 9.2% ($p=0.014$) and 7.3% versus 11.2% ($p=0.03$), respectively [78]. Adenosine can be considered to be an effective adjunctive therapy that minimizes infarct size and clinical events in patients with anterior infarcts treated with reperfusion therapy within 3–4 h of chest pain onset.

Nicorandil

Nicorandil is another molecule that has the potential to limit reperfusion injury [79]; this hybrid of an ATP-sensitive potassium-channel activator and a nitrate contributes to the reduction in preload and afterload, works as an ROS scavenger, and has neutrophil-modulating properties. The opening of potassium-ATP channels is known to be involved in preconditioning and postconditioning (see Part I). In two randomized studies, patients undergoing pPCI received nicorandil by intravenous infusion (4 mg bolus plus 6 mg/h for six hours) [80], or by a combination of intracoronary administration (1–2 mg) and intravenous administration (4 mg bolus plus 6 mg/h for 16 h) [81]; in both studies, patients who received nicorandil had a better final flow, a greater ST-segment resolution and fewer major clinical events, including deaths. The strategy of combining intracoronary and intravenous drug administration appears to be the most effective.

Postconditioning or modified reperfusion

Jakob Vinten-Johansen's group (Atlanta, USA) has probably launched a new era in the treatment of reperfusion injury and the protection of ischaemic but viable myocardium (see Part I). This group has demonstrated that gradual and haemodynamically controlled reperfusion is more effective than abrupt 'off-on' artery reopening, and has transformed preconditioning from a random phenomenon to a feasible therapeutic strategy that may become established as a second stage in STEMI reperfusion treatment.

Postconditioning reduces infarct size, preserves vascular endothelial function, decreases polymorphonuclear neutrophil accumulation and activation, decreases calcium overload, delays the restoration of neutral pH, reduces

apoptosis, inhibits ROS production and decreases cellular oedema. Hence, mechanical manipulation of the early phase of reperfusion can reduce post-ischaemic endothelial and myocardial injury, while providing conclusive proof of the existence of reperfusion injury. The first randomized clinical study showed that postconditioning during pPCI saved 32% of enzyme release, and turned a laboratory curiosity into a successful clinical application [13].

Proposals for the mechanisms underlying the efficacy of postconditioning have come from molecular biology studies. Yellon's group has shown that it is possible to protect reperfused myocardium by activating the prosurvival kinase signalling pathway, now called the reperfusion injury salvage kinase (RISK) pathway (see Part I). The effectors of these salvage kinases are the recently discovered mitochondrial transition pores (MTPs) and potassium-ATP channels. When opened (an effect promoted by calcium overload, oxidative stress and ATP depletion), MTPs lose their mitochondrial protective role, causing mitochondria to undergo massive swelling, and to become uncoupled and unable to maintain pH gradient and membrane potential; instead of producing ATP they start to degrade residual ATP. A second consequence of mitochondrial swelling is mitochondrial inner membrane architectural changes that result in the release of cytochrome c, which in turn activates proapoptotic caspases. The first postconditioning mechanism seems to prevent MTP opening and to preserve mitochondrial function. The second effector of postconditioning may be the opening of mitochondrial potassium-ATP channels, provoking a partial mitochondrial membrane depolarization and preventing calcium overload. The opening of potassium-ATP channels in sarcoplasmic reticulum may also decrease calcium overload and hence prevent myofibrillar contracture.

Not all of the signalling molecules that induce salvage pathways are known, although adenosine is recognized as being one of these triggers. The postconditioning technique may slow down adenosine washout by 'ramped' reperfusion. Bradykinin, which is synthesized during ischaemia, may also initiate salvage mechanisms. Other drugs that mimic postconditioning, such as opioids, insulin, cyclosporin A, angiotensin inhibitors, glucagon-like peptide-1, erythropoietin, statins, cardiotrophin-1, protein kinase C and transforming growth factor beta-1, may also activate these pathways and/or inhibit apoptosis directly by blocking caspases [82]. Some of these drugs (cyclosporin A, insulin and opioids) may be in clinical use in this setting in the near future.

Minimalist and low pressure reperfusion

A novel strategy has been proposed recently, based on the hypothesis that achieving a TIMI grade 3 flow (having crossed the occlusion with the wire or a small balloon, but leaving the stenosis), postponing the implantation of a stent for 12–24 h and preventing reocclusion with strong antithrombotic treatment, might protect myocardium against reperfusion injury [83]. Such a scheme results in low distal pressure reperfusion, delays washout, decreases mechanical stretch and may mimic postconditioning. Indeed, low pressure reperfusion is known to induce the RISK pathway, suggesting that such minimalist reperfusion might be comparable with postconditioning. In a pilot, non-randomized study of minimalist reperfusion, ST-

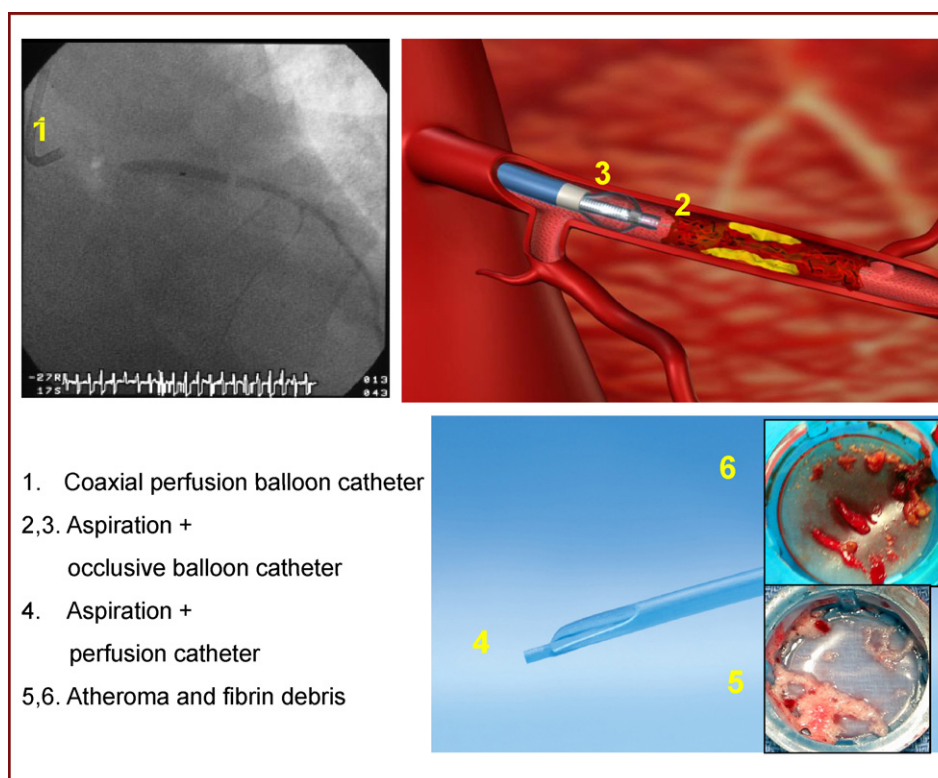


Figure 6. PCI tools available for the prevention and treatment of reperfusion injury: (1) coaxial perfusion balloon catheter allowing drug infusion; (2 + 3) thrombus aspiration and occlusive balloon catheter permitting simultaneous thrombus aspiration and postconditioning; (4) thrombus aspiration and perfusion catheter without balloon (5,6).

segment resolution (> 50%) at 60 min was achieved in 84% of patients [83].

Practical issues

Having convinced interventional cardiologists that the use of an 'off-on' pPCI technique can kill many viable endothelial and cardiomyocytes cells, how can we now transform experimental and preliminary clinical data into a viable modified reperfusion technique for clinical use? Two concepts must be taken into consideration: firstly, that the time window for reperfusion injury prevention starts at the first minute of reperfusion but extends over the next few hours (see Part I); secondly, that thrombus removal and postconditioning are counteractive – starting desobstruction with thrombus aspiration causes abrupt myocardial reflow, while starting with mechanical postconditioning can induce thrombus migration.

Pharmacological strategies must therefore be used with pPCI, including glycoprotein IIb/IIIa receptor blockade and possibly high-dose adenosine, and new drugs may be developed for this purpose in the near future. In addition, both thrombus aspiration and mechanical postconditioning may be integrated into the pPCI procedure; under these circumstances, new tools will have to be developed and tested to ensure that distal embolizations are prevented and that salvage pathways are induced (Fig. 6) [66].

Unresolved issues and future options

Current data demonstrate that while there is no unique 'magic bullet' for preventing reperfusion injury, a variety of therapeutic options do exist. If postconditioning is adopted as the principal strategy it will be necessary to identify the optimal sequences for balloon inflations and deflations (length and number), as differences can exist between animal models and humans. The question remains as to whether the postconditioning technique must be driven by ST-segment monitoring and prolonged until a significant decrease in ST-segment elevation is achieved.

In the future, pharmacological postconditioning may be adopted via the intravenous route or intracoronary injection. Intravenous pharmacological postconditioning may also be beneficial for patients treated with thrombolytic therapy. Finally, pharmacological reperfusion injury treatment must be continued for a number of hours to counteract the second delayed window for reperfusion injury.

Conclusion

Reperfusion injury is a proven event, occurring immediately after coronary reopening in STEMI patients but enduring thereafter. Prevention of reperfusion injury might optimize myocardial salvage, acting on the vascular bed as well as on cardiomyocytes. Glycoprotein IIb/IIIa receptor blockers and adenosine are two pharmacological treatments that are applicable immediately, as are thrombus aspiration and

mechanical modified reperfusion (postconditioning), provided that both of these strategies can be used almost simultaneously. More trials are needed, but a new era of myocardial reperfusion is certainly starting, dedicated not only to the epicardial artery but also to microvascular reperfusion and cardiomyocyte salvage. On-line ST-segment monitoring, available in every cath lab, provides an excellent means of measuring the immediate effects of such therapies.

Funding

No funding.

Conflict of interest

No conflict of interest.

References

- [1] Monassier JP, Valeix B, Guarino L, et al. Accentuation of myocardial ischemia during coronary recanalization in the acute phase of myocardial infarction. *Arch Mal Coeur Vaiss* 1984;77:1456–61.
- [2] Monassier JP, Valeix B, Collet F, et al. Electro-mechanical dissociation concomitant with myocardial reperfusion in the acute phase of myocardial infarction. *Arch Mal Coeur Vaiss* 1987;80:1423–7.
- [3] Monassier JP, Gressin V, Louvard Y, Hanssen M, Levy J, Katz O. Myocardial reperfusion syndrome. *Arch Mal Coeur Vaiss* 1992;85:743–50.
- [4] Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146–9.
- [5] Krug A, Du Mesnil de R, Korb G. Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 1966;19:57–62.
- [6] Kloner RA, Ganote CE, Jennings RB. The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974;54:1496–508.
- [7] Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of ‘no-reflow’ after percutaneous coronary intervention. *Circulation* 1994;89:2514–8.
- [8] Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992;85:1699–705.
- [9] Forman MB, Perry JM, Wilson BH, et al. Demonstration of myocardial reperfusion injury in humans: results of a pilot study utilizing acute coronary angioplasty with perfluorochemical in anterior myocardial infarction. *J Am Coll Cardiol* 1991;18:911–8.
- [10] Stone GW, Brodie BR, Griffin JJ, et al. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction (PAMI) stent pilot trial. *Circulation* 1999;99:1548–54.
- [11] Wang QD, Pernow J, Sjöquist PO, Ryden L. Pharmacological possibilities for protection against myocardial reperfusion injury. *Cardiovasc Res* 2002;55:25–37.
- [12] Limbruno U, Micheli A, De Carlo M, et al. Mechanical prevention of distal embolization during primary angioplasty: safety, feasibility and impact on myocardial reperfusion. *Circulation* 2003;108:171–6.
- [13] Staat P, Rioufol G, Piot C, et al. Postconditioning the human heart. *Circulation* 2005;112:2143–8.
- [14] Schofer J, Montz R, Mathey DG. Scintigraphic evidence of the “no-reflow” phenomenon in human beings after coronary thrombolysis. *J Am Coll Cardiol* 1985;5:593–8.
- [15] Bates ER, Krell MJ, Dean EN, O'Neill WW, Vogel RA. Demonstration of the “no-reflow” phenomenon by digital coronary arteriography. *Am J Cardiol* 1986;57:177–8.
- [16] TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985;312:932–6.
- [17] Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879–88.
- [18] van't Hof AW, Liem A, Suryapranata H, et al., Zwolle Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation* 1998;97:2302–6.
- [19] Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. *Circulation* 1993;87:1829–39.
- [20] Appleby MA, Angeja BG, Dauterman K, Gibson CM. Angiographic assessment of myocardial perfusion: TIMI myocardial perfusion (TMP) grading system. *Heart* 2001;86:485–6.
- [21] De Luca G, van't Hof AW, de Boer MJ, et al. Impaired myocardial perfusion is a major explanation of the poor outcome observed in patients undergoing primary angioplasty for ST-segment-elevation myocardial infarction and signs of heart failure. *Circulation* 2004;109:958–61.
- [22] Bowers TR, O'Neill WW. Beyond TIMI III flow. *Circulation* 2000;101:2332–4.
- [23] Hayat SA, Senior R. Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J* 2008;29:299–314.
- [24] Sakuma T, Hayashi Y, Sumii K, Imazu M, Yamakido M. Prediction of short- and intermediate-term prognoses of patients with acute myocardial infarction using myocardial contrast echocardiography one day after recanalization. *J Am Coll Cardiol* 1998;32:890–7.
- [25] Galiuto L, Garramone B, Scara A, et al. The extent of microvascular damage during myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling: results of the multicenter AMICI study. *J Am Coll Cardiol* 2008;51:552–9.
- [26] Santoro GM, Valenti R, Buonamici P, et al. Relation between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. *Am J Cardiol* 1998;82:932–7.
- [27] Poli A, Fèveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty. Real time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. *Circulation* 2002;106:313–8.
- [28] Fearon WF, Shah M, Ng M, et al. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2008;51:560–5.
- [29] Iwakura K, Ito H, Takiuchi S, et al. Alternation in the coronary blood flow velocity pattern in patients with no reflow and reperfused acute myocardial infarction. *Circulation* 1996;94:1269–75.
- [30] Lepper W, Hoffmann R, Kamp O, et al. Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction. *Circulation* 2000;101:2368–74.
- [31] Rezaizadeh-Bourdariat K, Lalande A, Ben Salem D, et al. Early study of myocardial perfusion with MRI in

- revascularized infarcts. *Arch Mal Coeur Vaiss* 2003;96:30–4.
- [32] Albert TS, Kim RJ, Judd RM. Assessment of no-reflow regions using cardiac MRI. *Basic Res Cardiol* 2006;101:383–90.
- [33] Jesel L, Morel O, Ohlmann P, et al. Role of pre-infarction angina and inflammatory status in the extent of microvascular obstruction detected by MRI in myocardial infarction patients treated by PCI. *Int J Cardiol* 2007;121:139–47.
- [34] Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J* 2001;22:729–39.
- [35] Feldman LJ, Coste P, Furber A, et al. Incomplete resolution of ST-segment elevation is a marker of transient microcirculatory dysfunction after stenting for acute myocardial infarction. *Circulation* 2003;107:2684–9.
- [36] Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation* 1989;80:1846–61.
- [37] Jeremy RW, Links JM, Becker LC. Progressive failure of coronary flow during reperfusion of myocardial infarction: documentation of the no reflow phenomenon with positron emission tomography. *J Am Coll Cardiol* 1990;16:695–704.
- [38] Rochitte CE, Lima JA, Bluemke DA, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. *Circulation* 1998;98:1006–14.
- [39] Tsunoda T, Nakamura M, Wakatsuki T, et al. The pattern of alteration in flow velocity in the recanalized artery is related to left ventricular recovery in patients with acute infarction and successful direct balloon angioplasty. *J Am Coll Cardiol* 1998;32:338–44.
- [40] L'Huillier I, Zeller M, Mock L, et al. Relation of hyperglycemia to ST-segment resolution after reperfusion for acute myocardial infarction (from Observatoire des Infarctus de Cote-d'Or Survey [RICO]). *Am J Cardiol* 2006;98:167–71.
- [41] Su H, Sun X, Ma H, et al. Acute hyperglycemia exacerbates myocardial ischemia/reperfusion injury and blunts cardioprotective effect of GIK. *Am J Physiol Endocrinol Metab* 2007;293:E629–35.
- [42] Iwakura K, Ito H, Ikushima M, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. *J Am Coll Cardiol* 2003;41:1–7.
- [43] Takahashi T, Hiasa Y, Ohara Y, et al. Relation between neutrophil counts on admission, microvascular injury, and left ventricular functional recovery in patients with an anterior wall first acute myocardial infarction treated with primary coronary angioplasty. *Am J Cardiol* 2007;100:35–40.
- [44] Giannitsis E, Muller-Bardorff M, Lehrke S, et al. Admission troponin T level predicts clinical outcomes, TIMI flow, and myocardial tissue perfusion after primary percutaneous intervention for acute ST-segment elevation myocardial infarction. *Circulation* 2001;104:630–5.
- [45] Antman EM, Cooper HA, Gibson CM, et al. Determinants of improvement in epicardial flow and myocardial perfusion for ST elevation myocardial infarction; insights from TIMI 14 and InTIME-II. *Eur Heart J* 2002;23:928–33.
- [46] Karila-Cohen D, Czitrom D, Brochet E, et al. Decreased no-reflow in patients with anterior myocardial infarction and pre-infarction angina. *Eur Heart J* 1999;20:1724–30.
- [47] Andrews J, Straznicky F, French JK, et al. ST-segment recovery adds to the assessment of TIMI 2 and 3 in predicting infarct wall motion after thrombolytic therapy. *Circulation* 2000;101:2138–43.
- [48] Sejersten M, Birnbaum Y, Ripa RS, et al. Influences of electrocardiographic ischaemia grades and symptom duration on outcomes in patients with acute myocardial infarction treated with thrombolysis versus primary percutaneous coronary intervention: results from the DANAMI-2 trial. *Heart* 2006;92:1577–82.
- [49] Kurisu S, Inoue I, Kawagoe T, et al. Impact of the magnitude of the initial ST-segment elevation on left ventricular function in patients with anterior acute myocardial infarction. *Circ J* 2004;68:903–8.
- [50] Kosuge M, Kimura K, Ishihawa T, et al. Relation of lateral ST-segment elevation pattern to myocardial salvage in patients with recanalized anterolateral acute myocardial infarction. *Clin Cardiol* 2004;27:106–11.
- [51] Kosuge M, Kimura K, Ishihawa T, et al. ST-segment depression in lead aVR: a useful predictor of impaired myocardial reperfusion in patients with inferior acute myocardial infarction. *Chest* 2005;128:780–6.
- [52] Birnbaum Y, Herz I, Sclarovsky S, et al. Prognostic significance of precordial ST segment depression on admission electrocardiogram in patients with inferior wall myocardial infarction. *J Am Coll Cardiol* 1996;28:313–8.
- [53] Wolak A, Yaroslavtsev S, Amit G, et al. Grade 3 ischemia on the admission electrocardiogram predicts failure of ST resolution and of adequate flow restoration after primary percutaneous coronary intervention for acute myocardial infarction. *Am Heart J* 2007;153:410–7.
- [54] McGehee JT, Rangasetty UC, Atar S, et al. Grade 3 ischemia on admission electrocardiogram and chest pain duration predict failure of ST-segment resolution after primary percutaneous coronary intervention for acute myocardial infarction. *J Electrocardiol* 2007;40:26–33.
- [55] Flaherty JT, Pitt B, Gruber JW, et al. Recombinant human superoxide dismutase (h-SOD) fails to improve recovery of ventricular function in patients undergoing coronary angioplasty for acute myocardial infarction. *Circulation* 1994;89:1982–91.
- [56] Zeymer U, Suryapranata H, Monassier JP, et al. The Na(+)/H(+) exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. Results of the evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI) trial. *J Am Coll Cardiol* 2001;38:1644–50.
- [57] Baran KW, Nguyen M, McKendall GR, et al., for the LIMIT AMI Investigators. Double blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction: limitation of myocardial infarction following thrombolysis in acute myocardial infarction (LIMIT AMI) study. *Circulation* 2001;104:2778–83.
- [58] Faxon DP, Gibbons RJ, Chronos NA, et al. The effect of blockade of the CD11/CD18 integrin receptor on infarct size in patients with acute myocardial infarction treated with direct angioplasty: the results of the HALT-MI Study. *J Am Coll Cardiol* 2002;40:1199–204.
- [59] Armstrong PW, Granger CB, Adams PX, et al. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2007;297:43–51.
- [60] Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 2002;23:1112–7.
- [61] Lefèvre T, Garcia E, Reimers B, et al. X-sizer for thrombectomy in acute myocardial infarction improves ST-segment resolution: results of the X-sizer in AMI for negligible embolization and optimal ST resolution (X AMINE ST) trial. *J Am Coll Cardiol* 2005;46:246–52.
- [62] Guetta V, Mosseri M, Shechter M, et al., UpFlow MI Study Investigators. Safety and efficacy of the FilterWire EZ in acute ST-segment elevation myocardial infarction. *Am J Cardiol* 2007;99:911–5.

- [63] Koch KT, Haeck JD, Van Der Schaaf RJ, et al. Proximal embolic protection with aspiration in percutaneous coronary intervention using the Proxis device. *Rev Cardiovasc Med* 2007;8:160–6.
- [64] Kunadian B, Dunning J, Vijayalakshmi K, Thornley AR, de Belder MA. Meta-analysis of randomized trials comparing anti-embolic devices with standard PCI for improving myocardial reperfusion in patients with acute myocardial infarction. *Catheter Cardiovasc Interv* 2007;69:488–96.
- [65] van't Hof AW, Liem A, de Boer MJ, Zijlstra F, Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *Lancet* 1997;350:615–9.
- [66] Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008;358:557–67.
- [67] Yip HK, Chen MC, Chang HW, et al. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. *Chest* 2002;122:1322–32.
- [68] Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695–701.
- [69] Petronio AS, Rovai D, Musumeci G, et al. Effects of abciximab on microvascular integrity and left ventricular functional recovery in patients with acute infarction treated by primary coronary angioplasty. *Eur Heart J* 2003;24:67–76.
- [70] Gabriel HM, Oliveira JA, da Silva PC, da Costa JM, da Cunha JA. Early administration of abciximab bolus in the emergency department improves angiographic outcome after primary PCI as assessed by TIMI frame count: results of the early ReoPro administration in myocardial infarction (ERAMI) trial. *Catheter Cardiovasc Interv* 2006;68:218–24.
- [71] Neumann FJ, Zohlnhöfer D, Fakhoury L, et al. Effect of glycoprotein IIb/IIIa receptor blockade on platelet-leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. *J Am Coll Cardiol* 1999;34:1420–6.
- [72] Huczek Z, Kochman J, Filipiak KJ, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2005;46:284–90.
- [73] Forman MB, Stone GW, Jackson EK. Role of adenosine as adjunctive therapy in acute myocardial infarction. *Cardiovasc Drug Rev* 2006;24:116–47.
- [74] Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000;101:2154–9.
- [75] Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999;34:1711–20.
- [76] Quintana JE, Hjemdahl P, Sollevi A, et al. Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis, results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003;59:1–9.
- [77] Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded placebo-controlled, multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005;45:1775–80.
- [78] Kloner RA, Forman MB, Gibbons RJ, et al. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J* 2006;20:2400–5.
- [79] Sakata Y, Kodama K, Komamura K, et al. Salutary effect of adjunctive intracoronary nicorandil administration on restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction. *Am Heart J* 1997;133:616–21.
- [80] Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol* 1999;33:654–60.
- [81] Ota S, Nishikawa H, Takeuchi M, et al. Impact of nicorandil to prevent reperfusion injury in patients with acute myocardial infarction: Sigmart Multicenter Angioplasty Revascularization Trial (SMART). *Circ J* 2006;70:1099–104.
- [82] Gross ER, Gross GJ. Ligand triggers of classical preconditioning and postconditioning. *Cardiovasc Res* 2006;70:212–21.
- [83] Isaaz K, Robin C, Cerisier A, et al. A new approach of primary angioplasty for ST-elevation acute myocardial infarction based on minimalist immediate mechanical intervention. *Coron Artery Dis* 2006;17:261–9.